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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/403,897 02/22/00 BARKAN

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EXAMINER

001444 HM12/0228  
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ART UNIT

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Please find below and/or attached an Office communication concerning this application or proceeding.

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<b>Office Action Summary</b>	Application No. 09/403,897  Examiner Karen Canella	Applicant(s)  <b>Barkan t al</b>  Group Art Unit 1642
<p><input type="checkbox"/> Responsive to communication(s) filed on _____</p> <p><input type="checkbox"/> This action is <b>FINAL</b>.</p> <p><input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> 35 C.D. 11; 453 O.G. 213.</p> <p>A shortened statutory period for response to this action is set to expire <u>3 months</u>, or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).</p>		
<p><b>Disposition of Claim</b></p> <p><input checked="" type="checkbox"/> Claim(s) <u>2-9 and 28-39</u> is/are pending in the application.</p> <p>Of the above, claim(s) _____ is/are withdrawn from consideration.</p> <p><input type="checkbox"/> Claim(s) _____ is/are allowed.</p> <p><input checked="" type="checkbox"/> Claim(s) <u>2-9 and 28-39</u> is/are rejected.</p> <p><input type="checkbox"/> Claim(s) _____ is/are objected to.</p> <p><input type="checkbox"/> Claims _____ are subject to restriction or election requirement.</p>		
<p><b>Application Papers</b></p> <p><input type="checkbox"/> See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.</p> <p><input type="checkbox"/> The drawing(s) filed on _____ is/are objected to by the Examiner.</p> <p><input type="checkbox"/> The proposed drawing correction, filed on _____ is <input type="checkbox"/> approved <input type="checkbox"/> disapproved.</p> <p><input type="checkbox"/> The specification is objected to by the Examiner.</p> <p><input type="checkbox"/> The oath or declaration is objected to by the Examiner.</p>		
<p><b>Priority under 35 U.S.C. § 119</b></p> <p><input type="checkbox"/> Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).</p> <p><input type="checkbox"/> All <input type="checkbox"/> Some* <input checked="" type="checkbox"/> None of the CERTIFIED copies of the priority documents have been received.</p> <p><input type="checkbox"/> received in Application No. (Series Code/Serial Number) _____.</p> <p><input type="checkbox"/> received in this national stage application from the International Bureau (PCT Rule 17.2(a)).</p> <p>*Certified copies not received: _____</p> <p><input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).</p>		
<p><b>Attachment(s)</b></p> <p><input checked="" type="checkbox"/> Notice of References Cited, PTO-892</p> <p><input type="checkbox"/> Information Disclosure Statement(s), PTO-1449, Paper No(s). _____</p> <p><input type="checkbox"/> Interview Summary, PTO-413</p> <p><input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review, PTO-948</p> <p><input type="checkbox"/> Notice of Informal Patent Application, PTO-152</p>		
<i>-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --</i>		

*Response to Amendment*

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Claims 1 and 10-27 have been deleted. Claims 28-39 have been added. Claims 2-9 and 28-39 are under consideration.

*New Claim Rejections*

3. Claims 2-9 and 28-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting tumor cell proliferation in vitro, does not reasonably provide enablement for a method of inhibiting tumor cell proliferation in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. An effective therapeutic protocol for the treatment or prevention of the formation of a tumor is subject to a number of factors which enter the picture beyond simply the specific binding of an antibody or a T cell line to the tumor cell line derived antigen. Demonstrating inhibition of cell growth by administration of leptin to cell lines growing in vitro cannot alone support the predictability of the method for treating a tumor growing in situ through administration of leptin. The establishment and growth of an in situ tumor is subject to variables beyond potential inhibition of growth stimulatory effects from IGF-1 and insulin on said tumor cells. The ability of a host to suppress and thereby prevent the tumor from establishing itself will vary depending upon factors such as the condition of the host, the type of tumor (rapidly proliferating or slowly proliferating) and the tumor burden. Furthermore, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening

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began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method comprising the administration of leptin, leptin muteins, and fragments and fusion proteins thereof would function as claimed based only upon the known mechanism of action of leptin on cells grown in culture. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). In addition, Hartwell et al (Science, 11997, 278:64-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited *supra*) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2). It appears that the instant formulations of the method are not selective for tumor cells nor would it be expected that the formulation would act only on

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dividing tumor cells since the leptin receptor occurs ubiquitously. In addition, anti-tumor agents must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with specific targeting. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated in vivo before producing a sufficient effect, for example, due to an inherently short half-life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

#### *Claim Rejections Maintained*

4. The rejection of claims 2-9 under 35 U.S.C. 112, first paragraph is maintained for reasons of record. The rejection of newly added claims 28-39 is made for the same reasons of record.

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Claims 2-9 and 28-39 are drawn in part to a method of treating tumors in a mammal comprising the administration of an effective amount of active agent selected from the group consisting of , a leptin mutein, a fragment of a leptin mutein, a fragment of leptin, a fusion protein comprising a fragment of a leptin mutein, and a leptin receptor antagonist. Applicant argues that the specification defines these leptin fragments and variants in the specification citing page 8, line 19 to page 9, line 3 as well as page 13, first paragraph and page 14, lines 21-25. These citations were considered but not found persuasive.

(A) As drawn to leptin muteins, proteins having at least 60%, 70% or 90% identity with the sequence of leptin, and fusion proteins thereof.

The instant claims are drawn to variants of the leptin protein. The specification has not demonstrated that leptin variants are capable of functioning as that which is suggested. The specification suggests, but does not demonstrate, that proteins which vary in the amino acids sequence of leptin, having at least 60%, 70% or 90% identity with leptin or leptin muteins, would function in the claimed method. Further embodiments included by claim 31 include a leptin mutant having a sequence encoded by a nucleic acid which hybridizes to the nucleic acid of leptin and has the ability to block cell proliferation. The specification defines muteins as analogs of leptin in which one or more amino acids are replaced without changing the activity of the protein. Neither the definition of "mutein" nor the claim to stringent hybridization serves to define the sequence of a variant product. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al. (J of Cell Bio. 111:2129-2138, 1990), replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology, 1988, Vol 8:1247-1252). These references demonstrate that even a single

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amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Clearly, it could not be predicted that a variant protein that shares only, for example, 60% sequence identity with leptin would even function as suggested. One of skill in the art would be subject to undue experimentation in order to find muteins and variants that function as leptin. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use variants and fusion proteins thereof. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

(B) As drawn to fragments of leptin, leptin muteins and fusion proteins thereof and antagonists of the leptin receptor.

The instant claims are drawn to an isolated polypeptide which comprises a small fragment of leptin or a leptin mutein and antagonists of the leptin receptor. Clearly, for the reasons given in paragraph 3 and paragraph 4(A) above, the specification is not enabling for a method based on the administration of an undisclosed leptin mutein, therefore the specification is not enabling for a method based on the administration of a fragment of said undisclosed leptin mutein. The specification does not demonstrate that a single fragment taken from the leptin protein would retain the growth inhibitory properties of the full length leptin protein and it would not be expected that elimination of parts of the amino acid sequence of leptin would not effect the function of the protein. For example it is well known in the art that proteins are folded 3-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry, 1996, pp. 165-171). In any given protein, amino acids distant from one another in the primary sequence may be closely located in the folded, 3-dimensional structure (Mathews and Van Holde, Biochemistry, 1996, pp. 166, figure 6.1). The specific conformation of a protein results from non-covalent interactions between amino acids, beyond what is dictated by the primary amino acid sequence. Absence of an amino

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acid sequence surrounding a fragment of the leptin protein can potentially radically alter the three dimensional structural environment of the fragment (Matthews, B. "Genetic and Structural Analysis of the Protein Stability Problem") thus, the consequences of the altered sequence environment cannot be predicted. Additionally, it is recognized in the art that protein function is context dependent, and cellular aspects, such as membrane anchorage, protein activation and sub-cellular location must be considered with respect to protein function in addition to molecular aspects (Bork, p. 398, col 2). Due to these reasons, one of skill in the art would be forced into undue experimentation in order to practice the invention as claimed.

5. All other rejections and objections as recited in Paper No. 7 are withdrawn.

#### *Conclusion*

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

February 11, 2001

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